## REMARKS/ARGUMENTS

The invention in this application involves the provision of a standard diluent for use in detecting target analytes in an immunoassay, in which two or more different target analytes are to be detected in a multiplex (i.e., simultaneous) assay. In preferred versions, the assay is aimed at detecting up to fifty or 100 different target analytes, preferably from two to fifty, or three to twenty, or four to fifteen, and in one example, eight different target analytes. The standard diluent of a biological fluid that is of a type that normally contains all the target analytes to be detected but, as present in the assay kit, is substantially free of these analytes.

The standard diluent that is substantially free of these target analytes is prepared from the appropriate biological fluid in one of two ways. In one embodiment (see, for example, claim 2), the biological fluid initially contains the target analytes, but they are substantially removed, for example by affinity chromatography, to produce the standard diluent that is included in the kit. In the other embodiment, the biological fluid is obtained from a host (for example, a human) whose biological fluid is already substantially free of the desired target analytes.

As stated in the specification, the term "substantially free" means that the target analytes either are undetectable by immunoassay methods, or that they are detectable, but are present in an amount below a selected sensitivity threshold.

Such standard diluents make possible the multiplex analyses for a plurality of target analytes ranging upwards from two to one hundred, or some intermediate number, as described in the specification, which contains an example showing the use of a standard diluent according to the invention in a procedure for detection of eight target analytes.

Claims 1-31 are under examination in this application. Newly added claims 49-60 should be examined with claims 1-31. Support for new claims calling for 2-100, 3-20 or 4-15 different target analytes is on page 6; support for claims calling for eight different target analytes is in the example.

Applicants note the inadvertent omission of some patent numbers in the previously submitted Information Disclosure Statement. These references are resubmitted in the accompanying Supplemental Information Disclosure Statement; consideration is

respectfully requested. Since the references have been placed in the application file, copies are not being provided at this time.

Claims 1- 18 are rejected under 35 U.S.C. 112 as indefinite. These claims have been amended to clarify any question, but the scope is not considered changed thereby. As described above, what is meant by the terminology is that the standard diluent is provided from a type of biological fluid that normally includes the two or more different target analytes to be detected in the multiplex assay. However, as it is present in the kit, the biological fluid is substantially free of these target analytes. That is because, as described in claims 2 and 3, either the fluid has been pretreated to remove the target analytes or because the fluid is obtained from a host (for example, a human) whose fluid in question is substantially free of these target analytes to begin with. As described on pages 4-5 of the specification, such hosts can be identified by screening a population for donors.

Claim 25 stands rejected as indefinite with respect to the mention of an undetectable endogenous level of target proteins. Claim 25 has been amended to state that the host's biological fluid is substantially free of the target analytes, which is considered to obviate any ambiguity in this claim.

Claim 3 is objected to as failing to limit the subject matter of a previous claim. The reason is not explicitly stated. Applicants submit that this claim does in fact limit claim 1 and is written in dependent form. It covers the embodiment where the standard diluent is prepared from the biological fluid of a host whose fluid is initially substantially free of the target analytes, as opposed to a fluid from which they have been removed, for example by affinity chromatography.

If the examiner still considers claim 3 objectionable, a more detailed explanation is respectfully requested.

Claims 1-3, 5-8, 11, 12 and 15-17 stand rejected as anticipated by Tamarkin et al.

Applicants respectfully controvert this rejection. Tamarkin et al. teach theremoval of only a single target analyte (IL-1 or IL-2) from a serum solution. Throughout the specification Tamarkin et al. refer to "a cytokine" and "the cytokine" but do not use the plural form. In column 16 (lines 37-42) Tamarkin et al. refer to preabsorption of IL-1 or IL-2

from a serum solution, but not of both. This statement is repeated at col. 17 lines 39-43. At col. 17 lines 14-22, parallel immunoassays are conducted for each of IL-1 and IL-2; note the term "both the IL-1 and IL-2 EIAs".

Tamarkin et al. thus do not anticipate any of the current claims.

Claims 2 and 4 are rejected as obvious over Tamarkin et al. in view of van Emon et al. The latter reference is cited for its disclosure of affinity chromatography to remove targets. However, as above, Tamarkin et al. do not disclose working with multiple target analytes, and van Emon et al. do not make up for this deficiency.

Claim 9 is rejected as obvious over Tamarkin et al. combined with Brailly et al., which is cited as disclosing certain of the target analytes. Again, however, the rejection is not well founded as neither reference discloses working with multiple target analytes.

Claims 10, 18 and 19 are rejected as obvious over Tamarkin et al. in view of Posner et al. The latter reference is cited for teaching mixing of two or more different target analytes to prepare controls or calibrants. However, Posner et al. do not use materials where target analytes have been removed or are initially substantially not present. Relevance of Posner et al. is not seen to kits and the like such as those claimed. Additionally, Posner et al. are directed to controls, not to standard diluents.

Claims 13, 14, 20-23, 25-28, 30 and 31 are rejected over Tamarkin et al. in combination with Chandler et al. Chandler et al. is directed to a series of differentiable beads. However, since Tamarkin et al. only disclose working with a single analyte, there would be no need for the use of differentiable beads in their process.

Claim 24 is rejected over the combination of Tamarkin et al. with Posner et al. and van Emon et al. Claim 29 is rejected as obvious over Tamarkin et al. in combination with Posner et al. and Brailly. However, for reasons mentioned above, these combinations do not render claims 24 and 29 obvious.

The references mentioned in the Office Action but not cited against the claims have been reviewed, and Applicants agree that they are not relevant to the claimed invention.

## CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 415-576-0200.

Respectfully submitted,

Joel G. Ackerman
Reg. No. 24,307

TOWNSEND and TOWNSEND and CREW LLP
Two Embarcadero Center, Eighth Floor
San Francisco, California 94111-3834
Tel: 415-576-0200
Fax: 415-576-0300
Attachments
JA:ja
60323652 v1